

2016 *Helicobacter pylori*: Global view***Helicobacter pylori* and colorectal neoplasia: Is there a causal link?**

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Abstract

Ever since *Helicobacter pylori* (*H. pylori*) was recognized as an infectious cause of gastric cancer, there has been increasing interest in examining its potential role in colorectal carcinogenesis. Data from case-control and cross-sectional studies, mostly relying on hospital-based samples, and several meta-analyses have shown a positive statistical relationship between *H. pylori* infection and colorectal neoplasia. However, the possibility exists that the results have been influenced by bias, including the improper selection of patients and disparities with respect to potential confounders. While the evidence falls short of a definitive causal link, it appears that infection with *H. pylori*/*H. pylori*-related gastritis is associated with an increased, although modest, risk of colorectal adenoma and cancer. The pathogenic mechanisms responsible for this association remain uncertain. *H. pylori* has been detected in colorectal malignant tissues; however, the possibility that *H. pylori* is a direct activator of colonic carcinogenesis remains purely hypothetical. On the other hand, experimental data have indicated a series of potential oncogenic interactions between these bacteria and colorectal mucosa, including induction and perpetuation of inflammatory responses, alteration of gut microflora and release of toxins and/or hormonal mediators, such as gastrin, which may contribute to tumor formation.

Key words: *Helicobacter pylori*; Colorectal cancer; Polyp; Adenoma; Gastrin

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Core tip: *Helicobacter pylori* (*H. pylori*) is a well-recognized gastric carcinogen; however, a causal

relationship with colorectal neoplasia remains uncertain. Data from case-control and cross-sectional studies, as well as several meta-analyses, have indicated a significant, although modest, statistical association between infection with *H. pylori*/*H. pylori*-related gastritis and the development of colorectal adenomas or cancer. Potential tumorigenic actions of *H. pylori* to colorectal mucosa include induction of inflammatory responses, alteration of gut microflora and release of toxins and/or hormonal mediators.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide and the fourth most common cause of cancer-related death, accounting for > 9% of all cancer incidence^[1-3]. Benign neoplastic polyps, namely tubular and villous adenomas, are premalignant lesions of the colon and rectum which have the potential to progress into invasive cancer^[4,5]. Colonic carcinogenesis is believed to be a multifactorial process; however, the direct etiology of CRC remains uncertain^[2]. Approximately 5%-10% of CRC cases arise as a consequence of recognized hereditary conditions, although the majority are sporadic forms in subjects without family history or any apparent predisposing condition^[6]. In addition to familial propensity and the influence of genetic factors, environmental factors, such as Western dietary practices, smoking, and alcohol consumption, have been linked to an increased risk of CRC^[7,8]. Unsurprisingly, given the sheer numbers of bacteria that populate the gastrointestinal tract, there has been growing interest in the relationship between infectious agents and colonic carcinogenesis.

Helicobacter pylori (*H. pylori*) is a ubiquitous human pathogen infecting approximately 50% of the population worldwide and up to 80% in developing countries^[9]. After colonizing the gastric mucosa, *H. pylori* induces chronic inflammation that culminate in the development of prevalent upper digestive disorders such as chronic gastritis and peptic ulcer disease^[10]. Moreover, *H. pylori* is a recognized class I carcinogen which plays a causal role in the development of gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma (MALT)^[11-13]. Ever since *H. pylori* has been established as the single infectious agent to cause gastric cancer, studies on its oncogenicity have been extended to examine its role in the development of other gastrointestinal malignancies. There is conflicting evidence on the relevance of chronic

infection by *H. pylori* as a risk factor for colorectal neoplasia. Indeed, some investigations have shown a statistical relationship^[14-20], disputed by others^[21-29].

The present article is aimed to a concise review on the possible causal relationship between *H. pylori* infection and colorectal neoplasia. Moreover, we discuss potential mechanisms by which the bacterium could exert oncogenic actions on the colonic mucosa. For these purposes, MEDLINE/PubMed was searched up to April 2015, using a combination of the following keywords: *H. pylori*, adenoma, colonic polyps, colorectal carcinoma, colorectal cancer, colon cancer and colonic neoplasms. We also reviewed the reference lists of all relevant articles retrieved in this search. Language was restricted to English and all data had to be published in a peer review journal.

H. PYLORI INFECTION STATUS AND COLORECTAL NEOPLASIA

Case-control studies

Several case-control studies have assessed the odds of colorectal neoplasia development with respect to *H. pylori* infection (Table 1). Occurrence of CRC has been the most commonly evaluated outcome, whereas seroprevalence relying on immunoglobulin G (IgG) detection has been the most common measure of *H. pylori* infection status. The results have been dramatically inconsistent, with some studies demonstrating a positive correlation^[14-20,30], in contrast to others showing null or inverse associations^[14,21-29]. This may be due to the fact that most of the studies suffered from inherent limitations including relatively small case samples (in most studies < 250 patients) and hospital-based design which may have resulted in patient selection bias. Two population-based studies, one conducted in Japan ($n = 478$)^[17] and another one from Germany ($n = 3381$)^[30], have both confirmed a significant correlation between *H. pylori* seroprevalence and the risk of colorectal adenomas and CRC respectively.

Evaluation based on serologic testing does not discriminate between current and past infections, a distinction likely to be relevant with respect to oncogenesis, and may yield positive results for *Helicobacter* species other than *H. pylori*^[31]. However, two studies relying on ¹³C-urea breath test (UBT) failed to demonstrate a relevant association with the risk of CRC^[26,32]. Contrarily, a Japanese study using a combination of three non-serological detection methods (UBT, rapid urease test and histology) pointed out a positive association with both colonic adenomas and CRC^[15]. Apart from methodological weaknesses relative to *H. pylori* detection, a series of other limitations may have had an influence on the results. Firstly, few of the investigations excluded patients with a history of *H. pylori* eradication therapy^[15,19], thus the cancerogenic risk may have

Table 1 Overview of case-control studies evaluating the odds of colorectal neoplasia development with respect to *Helicobacter pylori* infection

Ref.	Cases/controls, <i>n</i>	Matching variables	Measure of <i>H. pylori</i> status	Outcome	Adjusted OR (95%CI)
Talley <i>et al</i> ^[20] , 1991, United States	80/252	Convenience sample	IgG	Cancer	1.17 (1.03-2.84)
Penman <i>et al</i> ^[26] , 1994, United Kingdom	42/34	Age, Gender	UBT	Cancer	1.31 (0.52-3.26)
Moss <i>et al</i> ^[25] , 1995, United States	41/41	Age, Gender, Race	IgG	Cancer	0.74 (0.30-1.79)
Meucci <i>et al</i> ^[18] , 1997, Italy	94/100	Age, Gender	IgG	Adenoma or Cancer	1.92 (1.08-3.43)
Thorburn ^[29] , 1998, United States ²	233/233	Age, Gender, Education, Region, Date	IgG	Cancer	1.02 (0.69-1.51)
Breuer-Katschinski <i>et al</i> ^[14] , 1999, Germany	98/98	Age, Gender	IgG	Polyp	2.10 (1.12-3.92)
Fireman <i>et al</i> ^[21] , 2000, Israel	51/51	Convenience sample	IgG	Cancer	2.43 (1.00-5.59)
Hartwich <i>et al</i> ^[16] , 2001, Poland	80/160	Age, Gender	IgG, UBT	Cancer	3.78 (1.89-7.53)
Shmueli <i>et al</i> ^[27] , 2001, Israel	67/92	Convenience sample	IgG, CagA	Cancer	1.35 (0.67-2.74)
Siddheshwar <i>et al</i> ^[28] , 2001, United Kingdom	189/179	Age, Gender, Social class	IgG	Cancer Polyp	1.1 (0.7-1.8) 1.3 (0.7-2.5)
Limburg <i>et al</i> ^[23] , 2002, Finland ²	118/236	Age, Gender ¹ , Study center, Date of serum collection	CagA, whole cell assay	Cancer	0.91 (0.53-1.55)
Fujimori <i>et al</i> ^[15] , 2005, Japan	481/188	Age	UBT, urease test, histological diagnosis	Adenoma Cancer	1.60 (1.18-2.02) 1.80 (1.28-2.32)
Inoue <i>et al</i> ^[17] , 2011, Japan ³	239/239	Age	IgG	Adenoma	2.52 (1.57-4.05)
Zhang <i>et al</i> ^[30] , 2012, Germany ³	1712/1669	Age, Gender, Colorectal risk factors, Former colorectal endoscopy	IgG, CagA	Cancer	1.22 (1.02-1.45)

¹Only male smokers were included in the study; ²Nested case-control study; ³Population-based case-control studies. Data refer to studies reporting ORs or information from which such measure could be inferred. IgG: Immunoglobulin G; UBT: Urea breath test; CagA: Cytotoxin-associated gene A; *H. pylori*: *Helicobacter pylori*.

been underestimated due to the inclusion of *H. pylori*-negative CRC cases formerly exposed to the bacterium. Secondly, misestimations may have occurred due to the lack of data regarding previous colonoscopy with polyp removal. Thirdly, these studies may have been hampered by disparities in factors reflecting the carcinogenic risk, as most investigations controlled solely for age and gender or relied on a convenience sample. A recent population-based study has highlighted the importance of proper adjustment: including 1712 incident colorectal cancer cases and 1669 controls, the age- and sex-adjusted OR was 1.30 (95%CI: 1.14-1.50)^[30]. However, adjustment for known CRC risk factors (country of birth, educational level, smoking, average lifetime physical activity and alcohol consumption, body mass index, diabetes, history of CRC in first-degree-relative, use of non-steroidal anti-inflammatory drugs and hormone replacement therapy in females) has decreased the OR to 1.26 (95%CI: 1.09-1.47), whereas a further reduction to 1.8 (95%CI: 1.02-1.45) was observed after additional adjustment for previous colorectal endoscopy. These relatively small ORs underscore the need for rigorous adjustment for confounders, as well as adequate statistical power, in studies assessing the relationship between gastric *H. pylori* infection and the risk of colorectal neoplasia.

Cross-sectional studies

In recent years, a number of cross-sectional hospital-based studies examined a possible association

between *H. pylori* infection and colorectal neoplasia. In an Asian study including 9311 asymptomatic subjects > 40 years, detection of *H. pylori* using biopsy urease testing was an independent predictor for colorectal adenoma (OR = 1.36, 95%CI: 1.23-1.52) after controlling for several confounders including gender, age, smoking and alcohol consumption^[33]. The study also pointed concomitant metabolic syndrome as a factor associated with a further increased risk of colorectal adenomas (OR = 1.41, 95%CI: 1.23-1.61). In a study with 2195 (1253 cases) asymptomatic average-risk subjects from South Korea, Hong *et al*^[34] determined a positive association between *H. pylori* seropositivity and the risk for overall (OR = 1.36, 95%CI: 1.10-1.68) and advanced (OR = 2.21, 95%CI: 1.41-3.48) adenoma after adjusting for several factors including a family history of CRC and regular use of aspirin. Similarly, a small (*n* = 273) study from Israel has pointed a positive association with both advanced colorectal neoplasia (adjusted OR = 9.57, 95%CI: 4.31-21.2) and CRC (adjusted OR = 7.98, 95%CI: 3.16-20.16)^[35]. In line with these previous reports, a study focusing on African-Americans (*n* = 1256), a population with a high burden of *H. pylori* infection^[36], found an increased risk of colorectal polyps in *H. pylori*-infected than non-infected subjects (OR = 1.95, 95%CI: 1.2-1.9)^[37]. However, results should be interpreted cautiously, as the authors did not perform adjustments for potential confounders. Contrarily, the association between *H. pylori* and colorectal adenomas was not relevant in a cohort of United States His-

Table 2 Published meta-analyses evaluating the relationship between *Helicobacter pylori* infection and the development of colorectal neoplasia

Ref.	Included studies, <i>n</i>	Outcome	Summary OR (95%CI)	Conclusion
Zumkeller <i>et al</i> ^[45] , 2006, Germany	11 ¹	Cancer	1.4 (1.1-1.8)	Possible small increase in the risk of CRC
Zhao <i>et al</i> ^[44] , 2008, China	13 ¹ (9 using IgG to detect infection status)	Cancer	1.49 (1.17-1.91)	Possible increase in risk of CRC
Hong <i>et al</i> ^[34] , 2012, South Korea	10	Adenoma	1.56 (1.14-2.14) evaluating IgG as the only test indicator)	Modest increase in the risk of colorectal adenoma
Wu <i>et al</i> ^[43] , 2013, China	27	Adenoma	1.66 (1.39-1.97)	Positive association between <i>H. pylori</i> and colorectal neoplasia
		Cancer	1.39 (1.18-1.64)	
Rokkas <i>et al</i> ^[42] , 2013, Greece	28	Polyps	1.50 (1.26-1.79)	Modest statistically significant relationship of <i>H. pylori</i> with both cancer and polyps
		Cancer	1.30 (1.07-1.59)	
Chen <i>et al</i> ^[46] , 2013, China	22	Cancer	1.49 (1.30-1.72)	<i>H. pylori</i> increases the risk of CRC
Guo <i>et al</i> ^[41] , 2014, China	9 ²	Hyperplastic polyp	0.72 (0.44-1.18)	No statistical association between <i>H. pylori</i> and colorectal neoplasm was found, but <i>H. pylori</i> may increase the risk of adenoma
		Adenoma	1.83 (1.35-2.51)	
		Cancer	1.08 (0.89-1.68)	

¹Only case-control studies were included; ²Included only data based on East-Asian population. *H. pylori*: *Helicobacter pylori*; IgG: Immunoglobulin G; CRC: Colorectal cancer.

panics^[38], a population in which the seroprevalence of *H. pylori* infection is high whilst the risk of CRC is relatively low^[39]. However, due to the multifactorial nature of CRC, epidemiological associations are difficult to draw and are not appropriate for establishing a causal effect. This may in turn be reflected in the fact that the geographical and temporal trends of CRC do not overlap with those of gastric cancer in many parts of the world (e.g., Japan, where the incidence rates of stomach cancer decline, in parallel with increasing incidence of CRC)^[40].

In conclusion, although many cross-sectional studies have outlined a positive association, the possibility exists that the results have been dramatically influenced by bias including improper selection of patients, retrospective reporting of data, and disparities with respect to several factors affecting the cancerogenic risk. Last but not the least, it should be emphasized that cross-sectional studies may only establish associations and are not relevant to prove causality.

Meta-analyses of published studies

At least seven meta-analyses have pooled data to evaluate the relationship between *H. pylori* infection and the development of colorectal neoplasia (Table 2)^[34,41-46]. In a 2006 meta-analysis, Zumkeller *et al*^[45] summarized data from 11 case-control studies (899 CRC cases, 1476 controls) and the pooled OR for CRC was 1.4 (95%CI: 1.1-1.8). However, different testing methods were combined to assess the *H. pylori* infection status. In a later analysis, Zhao *et al*^[44] included a total of 13 case-control studies and found comparable results (OR = 1.49, 95%CI: 1.17-1.91). Nonetheless, the authors performed a separate analysis of ten studies using IgG response as the only testing method, the results of which revealed a

slightly higher OR (1.56, 95%CI: 1.14-2.14). More recent meta-analyses combined data from both case-control and cross-sectional studies to evaluate *H. pylori* in relation to colorectal adenomas. In a meta-analysis of ten studies (15,863 subjects), including their own cross-sectional study, Hong *et al*^[34] found that the pooled OR for colorectal adenoma related to *H. pylori* infection was 1.58 (95%CI: 1.32-1.88). In 2013, three updated meta-analyses, each one comprising more than 20 studies, confirmed a positive association between *H. pylori* infection and CRC or adenoma^[42,43,46]. Nonetheless, by analyzing a total of 16 sets of data, Rokkas *et al*^[42] pointed out a statistically significant relationship between *H. pylori* infection and colon polyps (OR = 1.5, 95%CI: 1.26-1.79).

Although meta-analyses converge to a modest positive association, results could have been influenced by inevitable heterogeneity among the included studies. Moreover, each of the analyses could incorporate the biases of the individual studies, discussed above. Notably, there is considerable overlap of underlying studies between the meta-analyses, with most of the data coming from Western countries, whilst Asian data mostly comes from Japan. Thus, concerns may arise about the generalizability of the results in other populations and/or geographical locations. Indeed, a recent meta-analysis based on East-Asian population (9 studies, 2081 cases and 5598 controls) questioned the association between *H. pylori* infection and the overall risk of colorectal neoplasia (hyperplastic polyps, adenomas and CRC), and only a heightened risk of developing colorectal adenoma was found (OR = 1.83, 95%CI: 1.35-2.51)^[41]. In regional sub-analysis the association between *H. pylori* infection and colorectal neoplasms was only significant in the Japanese population though, as noted by the authors, significant statistical heterogeneity limited the conclusions.

H. PYLORI-RELATED CHRONIC GASTRITIS AND COLORECTAL NEOPLASIA

Sonnenberg *et al.*^[47] conducted the largest case-control study to date, aiming to determine the association between *H. pylori*-related gastritis and colorectal neoplasia. Using a national database of surgical pathology reports from the United States, the authors analyzed 156000 patients (mean age: 58.7 years, 41% males) who underwent bidirectional endoscopy on the same day with biopsies from both procedures^[47]. *H. pylori* gastritis was defined as chronic active inflammation in the gastric mucosa with presence of *H. pylori* organisms demonstrated by immunohistochemistry. According to the results, patients with *H. pylori* gastritis were more likely than patients without *H. pylori* to have hyperplastic polyps (OR = 1.24, 95%CI: 1.18-1.30), adenomatous polyps (OR = 1.52, 95%CI: 1.46-1.57), advanced adenomas (OR = 1.80, 95%CI: 1.69-1.92), villous adenomas or adenomas with high-grade dysplasia (OR = 1.97, 95%CI: 1.82-2.14) and adenocarcinomas (OR = 2.35, 95%CI: 1.98-2.80). Noticeably, the risk was found to increase with advancing stage of the colorectal neoplasm and in relation with the size and number of the adenomas.

Use of histopathological data and the large sample are major strengths of the study by Sonnenberg *et al.*^[47]. However, results should be interpreted cautiously due to several limitations^[48]. These include: (1) the study only included a sample of subjects undergoing endoscopy, which may not be representative of the general population; (2) the results were not adjusted for confounders such as gender, age and previous use of antisecretory agents and/or antibiotics; and (3) case-control studies are not adequate to establish causal associations.

H. PYLORI-RELATED GASTRIC PREMALIGNANT LESIONS AND COLORECTAL NEOPLASIA

To date, inconsistent data has been provided to support a causal link between progression to chronic atrophic gastritis and colorectal tumorigenesis. Two Japanese case-control studies with 339^[24] and 478^[17] subjects found no significant association between chronic atrophic gastritis diagnosed on the basis of serum pepsinogen (PG)-I and PG-I/II ratio (diagnostic criteria: PG-I \leq 70 ng/mL and PG-I/II \leq 3) and colorectal neoplasia. Including 20928 Finnish male smokers (age range: 50-69 years old) participating in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), there was no increased risk of CRC among those with low PG-I levels ($<$ 25 μ g/L; n = 1665) and among those with biopsy-proven atrophic gastritis (n = 1006) during a mean follow-up of 11.3

years^[49]. Similarly, hypergastrinemic atrophic gastritis patients aged $>$ 40 years (n = 160) did not have a higher probability of developing CRC when compared to age- and gender-matched normogastrinemic controls with normal gastric histology in a study from Italy^[50]. In contrast to these previous observations, a recent report (n = 99) showed a higher risk of recurrence of endoscopically-resected colorectal neoplasia in patients with both a positive *H. pylori* serology and low PG levels^[51].

The only evidence to date supporting a positive association between gastric intestinal metaplasia and the risk of colonic neoplasms comes from the large case-control study by Sonnenberg *et al.*^[47]. The following conditions in the colon were all found more frequently in patients with (n = 5651) than without intestinal metaplasia: colon adenoma (OR = 1.82, 95%CI: 1.71-1.94), advanced adenoma (OR = 2.02, 95%CI: 1.82-2.24) and CRC (OR = 2.55, 95%CI: 1.93-3.37) development^[47]. The magnitude of this association was at least similar, if not higher, in comparison to *H. pylori* gastritis. Interestingly, advanced gastric lesions such as gastric adenoma and gastric cancer or lymphoma were even more strongly associated with CRC (OR = 2.84, 3.18 and 4.54 respectively). The authors did not analyze data with respect to atrophic gastritis due to the absence of multiple mapped gastric biopsy specimens required to diagnose this condition.

In summary, no solid conclusions can be drawn as yet on whether progression to gastric precancerous conditions (*i.e.*, chronic atrophic gastritis and gastric intestinal metaplasia) could enhance the risk of neoplastic transformation in the colon. Well-designed studies are warranted to clarify the existence of a potential link between colonic carcinogenesis and the presence, extent and/or histopathological severity of gastric conditions related to *H. pylori* infection.

ASSOCIATIONS ACCORDING TO SITE AND HISTOLOGY OF COLONIC NEOPLASMS

Previous studies have examined the relationship between *H. pylori* infection and the location of colorectal neoplasia, providing conflicting results. Zhang *et al.*^[30] have postulated that the CRC risk elevation associated with *H. pylori* infection was essentially limited to the left colorectum with an OR of 1.22 (95%CI: 1.02-1.45). Contrarily, Hong *et al.*^[34] supported the same for proximal neoplasms, whereas no location-based differences were found in other studies^[15,37,38]. Experimental data based on animal models have indicated that the mitogenic action of gastrin, a putative trophic factor for colorectal mucosa, is selective for the distal colon^[52-55]. Congruently, an association between hypergastrinemia and distal distribution of adenomas was determined in

a prospective case-control study^[22]. On the other hand, enhanced production of bile acids secondary to colonic bacterial overgrowth, resulting in aberrant DNA methylation, has been considered to increase the risk of proximal CRC^[56,57]. Using serum PG levels as a marker, Inoue *et al*^[17] determined that the proximal adenoma risk increased stepwise with the presence and progression of *H. pylori*-related chronic gastritis, showing a maximal increase in association with chronic atrophic gastritis. Contrarily, this last condition appeared to imply no further risk with respect to distal adenomas. Unlike previous observations highlighting site-selective variations, the association between histologically-proven *H. pylori*-positive gastritis and the occurrence of colonic neoplasms was shown to be similar across different locations of the large bowel^[47].

Similarly to location issues, histology-based associations remain inconclusive. Using immunohistochemical methods Soylu *et al*^[58] have demonstrated that the prevalence of *H. pylori* was higher in villous type polyps. Oppositely, Jones *et al*^[59] showed significant associations between *H. pylori* prevalence and tubular, tubulovillous adenomas and CRC cases, but not with villous adenomas. According to Hong *et al*^[34], *H. pylori* seropositivity was more strongly associated with the presence of advanced adenomas (OR = 2.21, 95%CI: 1.41-3.48 vs 1.36, 95%CI: 1.10-1.68 for overall colorectal adenoma), whereas Sonnenberg *et al*^[47] noticed a trend for the strength of the associations to increase between *H. pylori*-related gastritis and increasing histopathological severity of the colonic neoplasms: hyperplastic polyps (OR = 1.42), adenomas (OR = 1.82), villous adenoma or dysplasia (OR = 2.17) and CRC (OR = 2.55). Contrarily, in a study including 1256 African Americans (366 *H. pylori*-positive; assessed by immunohistochemistry on gastric specimens) the histology of colonic adenomas (advanced vs non-advanced) was not substantially related to *H. pylori* status^[37].

POTENTIAL ONCOGENIC ACTIONS OF *H. PYLORI* TO COLORECTAL MUCOSA

Several pathogenetic mechanisms have been put forward to explain the possible causal link between *H. pylori* infection and colorectal neoplasia. Persistent *H. pylori* exposure elicits hypergastrinemia, which is a putative trophic factor for the colorectal mucosa and thereby a plausible promoter of mutagenesis^[60]. Indeed, gastrin has been shown to be directly mitogenic on either normal or neoplastic colonic cells *in vitro*, whereas non-amidated gastrins resulted in hyperproliferation of colonic mucosa in transgenic mice^[61-65]. However, although both *in vitro* and *in vivo* data seem to confirm the tumorigenic properties of gastrin and its derivatives, this association still remains unclear in humans. Several reports, including two prospective studies^[22,29], confirmed a statistical relationship between

elevated serum/plasma gastrin levels and an increased risk of colorectal adenoma and/or CRC^[16]. However, this notion was disputed by other studies^[21,24,26,66,67]. Critically, differences in gastrin levels attributable to PPI use, variable follow-up duration and exclusive measurement of amidated forms of gastrin may have accounted for the conflicting results. Moreover, other human models of long-term hypergastrinemia, such as use of PPIs and Zollinger-Ellison syndrome, showed no effect on the development of colonic adenomas or CRC^[68,69]. Remarkably, CRC tumor cells have been shown to secrete gastrin themselves which likely act in an autocrine manner^[70-72]. Under this assumption, the hypergastrinemia observed in CRC patients is likely the epiphenomenon of gastrin secretion by tumor cells and, indeed, a fall in serum/plasma levels of gastrin has been observed following surgical resection of CRC^[73,74]. Taken together, these data support a role of gastrin, but not plainly a relation with *H. pylori*, in the development of colorectal neoplasia^[22].

Reduced gastric acid secretion secondary to *H. pylori*-related chronic atrophic gastritis might contribute to colorectal carcinogenesis by promoting changes in the colorectal microflora^[75,76]. It has been postulated that a selective growth of certain microbial species, such as *B. fragilis* and *E. faecalis*, may promote the development of CRC^[77-79]. In a recent report including 60 patients with CRC and 119 controls, Sobhani *et al*^[80] demonstrated a significant association between CRC and microbial dysbiosis, showing that the quantitative polymerase chain reaction (qPCR) values for *Bacteroides/Prevotella* were higher in CRC patients as compared to controls. Noticeably, the odds of CRC development in patients undergoing gastric surgery for peptic ulcer disease, another condition associated with a hyposecretory state, remain inconclusive^[81-84].

H. pylori is not an invader of the colonic epithelium, nor it is known to reside in the colonic mucosa. However, it moves through the colonic lumen, as indicated by reports of fecal shedding of viable *H. pylori*^[85]. Thus, local activation of colonic carcinogenesis may be hypothesized. In this regard, several authorities have reported detection of *H. pylori* organisms by immunohistochemistry in neoplastic colorectal tissues. Soylu *et al*^[58] reported a positive *H. pylori* staining in 11 out of 51 (21.6%) colonic polyps (31 tubular adenomas), whereas this rate was 1.7% for normal specimens, 15.3% for adenomas and 16.9% for CRC in a series by Jones *et al*^[59] including 176 specimens. Similarly, using cresyl violet staining and immunohistochemistry, Kapetanakis *et al*^[86] reported detection of *H. pylori* organisms in 64% and 84% of polyp ($n = 25$) and CRC ($n = 50$) specimens respectively. False positive results cannot be precluded by immunohistochemistry, thus some authors employed PCR analysis for detection of *H. pylori* genomic material in colorectal tissue. Grahm *et al*^[87] detected *H. pylori* DNA in 27% of CRC specimens, comparable to 22% among patients undergoing colonoscopy for nonspecific

gastrointestinal disturbances^[31]. Another study by Bulajic *et al.*^[88] found that only 1.2% of malignant colorectal tissue samples were positive for *H. pylori*, compared with 6% of normal tissues.

Infection with virulent strain of *H. pylori* that express CagA gene may contribute to colorectal carcinogenesis by inducing enhanced inflammatory responses, including overproduction of cytokines such as IL-8, a known growth factor for human CRC^[89]. Moreover, infection with CagA-positive *H. pylori* is associated with higher levels of gastrin and a higher likelihood of progression to chronic atrophic gastritis^[90,91]. To date, at least four studies have determined a positive association between CagA seropositivity and colorectal neoplasia^[16,22,27,67], while other found no correlation^[23,45,92]. As in the case of gastric adenocarcinoma, additional bacterial factors might be able to drive colonic carcinogenesis through the induction of inflammatory responses and promotion of neo-angiogenesis^[93]. Interestingly, gastric cancer stem cells (CSCs) and recruited bone marrow-derived cells (BMDCs) have been shown to contribute to gastric cancer formation in a mouse model of chronic helicobacter infection^[94]. Noteworthy, preliminary data suggested increase expression of CD44 (a marker of human hematopoietic stem cells and CSCs) in 78% and 16% of patients with CRC and colorectal polyps respectively^[86]. Thus, a potential oncogenic action of *H. pylori* to colorectal mucosa mediated by the induction of a chronic inflammatory process, CSCs stimulation, and recruitment of BMDCs warrants further robust assessment.

CONCLUSION

Since more than two decades, several studies investigated the potential association between *H. pylori* infection and colorectal neoplasia. However, most investigations relied on relatively small hospital-based samples providing conflicting results. In more recent years, better designed population-based studies, as well as the large-scale histological series by Sonnenberg and Gienta and relevant meta-analyses have become available. Nevertheless, results should be interpreted cautiously as the possibility of bias cannot be excluded. Based on a critical analysis of available data, it appears that *H. pylori* infection/*H. pylori*-related gastritis is associated with an increased, although modest, risk of colorectal adenoma and/or CRC. However, it should be emphasized that current evidence supports nothing more than a statistical relationship, whilst a definitive proof of causality remains to be established. Similarly, it is not yet possible to determine prognostic associations between the risk of colonic neoplasia and the extent and/or histopathological severity of the gastric lesions related to *H. pylori* infection. A potential direct activation of colorectal carcinogenesis by the bacterium remains to be elucidated, as detection of the pathogen in

malignant tissues, either by immunohistochemistry or PCR analysis, does not prove causality. On the other hand, experimental data have indicated a series of potential oncogenic interactions between *H. pylori* and colorectal mucosa, including induction and perpetuation of inflammatory responses, alteration of gut microflora and release of toxins and/or hormonal mediators which may contribute to tumor formation. In the future, large-scale studies with rigorous methodology are awaited to confirm *H. pylori* as an infectious contributor in the complex multifactorial process of colorectal tumorigenesis.

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